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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,107	05/23/2005	Charlotta Olsson	4055-1002	5068

466 7590 11/20/2009

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EXAMINER	
CROW, ROBERT THOMAS	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
11/20/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketingDept@young-thompson.com

Office Action Summary	Application No.	Applicant(s)	
	10/510,107	OLSSON ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-25,27-34 and 36-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-25,27-34 and 36-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's after-final submission filed on 30 September 2009 and the submission filed with the Request for Continued Examination of 9 November 2009 have both been entered.

Status of the Claims

2. This action is in response to Applicant's amendments filed 30 September 2009 in which claims 19, 27, 33, and 42 were amended, no claims were canceled, and no new claims were added and in response to Applicant's amendments filed 9 November 2009 in which the specification was amended, claims 19, 32-33, and 41-42 were amended, no claims were canceled, and new claims 43-47 were added.

Both the amendments filed 30 September 2009 and the amendments filed 9 November 2009 have been thoroughly reviewed and entered.

The objections to the claims listed in the previous Office Action are withdrawn in view of the amendments.

The objection to the specification listed in the previous Office Action is withdrawn in view of the amendments. However, new objections necessitated by the amendments are presented below.

The previous rejections under 35 U.S.C. 112, first paragraph, are withdrawn in view of the amendments. However, new rejections necessitated by the amendments are presented below.

The previous rejections under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendments.

The previous rejections 35 U.S.C. 103(a) are maintained. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections.

Claims 19-25, 27-34, and 36-47 are under prosecution.

Specification

3. The amendment filed 9 November 2009 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. This is a new objection necessitated by the amendments. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicant has added the generic terminology "nonionic surfactant." As evidenced by page 348 of the 1998 Calbiochem general catalog and by pages 257-258 and 262 of the 2000-2001 Sigma Catalog, while NP-40, Tween 20, and Triton X-100 are nonionic surfactants, the generic terminology "nonionic surfactant" encompasses the entire genus of nonionic surfactants. A review of the specification yields no recitation of either "nonionic" or "surfactant," nor does the specification recite any other specific detergents that are surfactants or nonionic. Thus, because the recitation "nonionic surfactant" encompasses a broad genus of compounds

not supported by the original disclosure, the recitation "nonionic surfactant" is new matter.

4. Applicant is required to cancel the new matter in the reply to this Office Action.

5. With respect to Tween 20 and Triton X-100, it is noted that pages 258 and 262 of the Sigma "Products for Life Science Research" Catalog (2000-2001; provided with this Office Action by the examiner) properly establish the chemical structures of the respective compounds at the time of filing. Applicant is encouraged to use the evidence presented in the 2000-2001 Sigma "Products for Life Science Research" Catalog for future amendments regarding Tween 20 and Triton X-100.

6. With respect to NP-40, it is noted that page 348 of the 1998 Calbiochem general catalog states lists two different structures for NP-40, each of which are different from the structure previously claimed by Applicant (see the Amendments filed 15 April 2009). It is further noted that the Material Safety Data Sheet (MSDS) provided online by aktasdis.com ([retrieved on 2009-11-17]; retrieved from the Internet: <URL: www. aktasdis.com/images/pdf/NP-40_MSDS.pdf>. Dated 10 February 2003) indicates that NP-40 is a nonylphenyl polyethylene glycol derivative. Thus, at the time of filing of the instant Application, at least two different and chemically distinct chemical compositions were available as "NP 40.

Therefore, given the ambiguity regarding the chemical structure of NP 40 at the time of filing of the instant Application, it is suggested that Applicant provide evidence of the source(s) of NP 40 used in the practice of the claimed invention so as to clearly

establish the chemical structure of the compound(s) used in practicing the instantly claimed method.

Claim Interpretation and Claim Objections

7. For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355 ("PPG could have defined the scope of the phrase consisting essentially of' for purposes of its patent by making clear in its specification what it regarded as constituting a material change in the basic and novel characteristics of the invention."). See also AK Steel Corp. v. Sollac, 344 F3.d 1234, 1239-1240, 68 USPQ2d 1280, 1283-84 (Fed. Cir. 2003); In re Janakirama-Rao, 317 F.2d 951, 954, 137 USPQ 893, 895-96 (CCPA 1963). See MPEP 2163.

8. In view of the interpretation of "consisting essentially of" as "comprising" as discussed in Section 4, Applicant is advised that should claims 19 or 44 be found allowable, claims 43 and 47 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). This is a new objection necessitated by the amendments.

Claim Rejections - 35 USC § 112, First Paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 32 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a new matter rejection necessitated by the amendments. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 32 and 41 have each been amended to recite "nonionic surfactant" in line 7 of each of he claims. As noted above, while page 348 of the 1998 Calbiochem general catalog and while pages 257-258 and 262 of the 2000-2001 Sigma Catalog, while NP-40, Tween 20, and Triton X-100 are nonionic surfactants, the generic terminology "nonionic surfactant" encompasses the entire genus of nonionic surfactants. A review of the specification yields no recitation of either "nonionic" or "surfactant," nor does the specification recite any other specific detergents that are surfactants or nonionic. Thus, because the limitation "nonionic surfactant" encompasses a broad genus of compounds not supported by the original disclosure, the limitation "nonionic surfactant" is new matter.

11. As noted above, it is reiterated that pages 258 and 262 of the Sigma "Products for Life Science Research" Catalog (2000-2001; provided with this Office Action by the examiner) properly establish the chemical structures of Tween 20 and Triton X-100 at the time of filing. Applicant is encouraged to use the evidence presented in the 2000-2001 Sigma "Products for Life Science Research" Catalog for future amendments regarding Tween 20 and Triton X-100.

12. It is also reiterated that given the ambiguity regarding the chemical structure of NP 40 at the time of filing of the instant Application (as evidenced by page 348 of the 1998 Calbiochem general catalog and the Material Safety Data Sheet (MSDS) provided online by aktasdis.com), it is suggested that Applicant provide evidence of the source(s) of NP 40 used in the practice of the claimed invention so as to clearly establish the chemical structure of the compound(s) used in practicing the instantly claimed method.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 19-25, 29, 31, 33-34, 38, 40, and 42-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Urdea et al (U.S. Patent No. 4,910,300, issued 20 March 1990).

Regarding claims 19 and 29, Quake et al teach a method comprising providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines

the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186) or by photobleaching (paragraph 0193), and the removal is prior to the next extension cycle (paragraph 0216). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

While Quake et al teach the labels are fluorescent labels and that the labels are cleaved via a cleavable linker arm (paragraph 0186), Quake et al do not explicitly teach a cleavable link between the label and the nucleotide that is a disulfide (i.e., claim 19) and the linker is shorter than 8 atoms (i.e., claim 29).

However, Urdea et al teach functionally equivalent labeled cleavable nucleotides (column 8, lines 20-60), wherein the detectable label is a fluorescent label (column 4, lines 5-10) and is linked to the nucleotide with a cleavable linker in the form of a disulfide linker (i.e., claim 19; column 8, lines 20-60). The linker between the disulfide bridge and the base is less than 8 atoms; namely, Formula 13 has label R1, a disulfide for R2, x is one CH2 linker, and NH connects to the base (i.e., claim 29; column 8, lines 20-60). Urdea et al further teach that the nucleotides having the linkers and labels have the added advantage of being inexpensively synthesized in large quantity (column 2, lines 15-40). Thus, Urdea et al teach the known technique of using a disulfide as a cleavable link between a label and a nucleotide.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of cleavable labeled nucleotides attached with a cleavable linker as taught by Quake et

al so that the labeled cleavable nucleotides are the functionally equivalent labeled cleavable nucleotides having a cleavable linker that is a disulfide linker (i.e., claim 19) that is less than 8 atoms (i.e., claim 29) as taught by Urdea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of having a decreased cost as a result of utilizing labels that are inexpensively synthesized in large quantity as explicitly taught by Urdea et al (column 2, lines 15-40). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et al could have been applied as the labeled cleavable nucleotides in the method of Quake et al with predictable results because the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et al predictably results in a link useful in the labeling of nucleotides.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not posses characteristic relied on" (205 USPQ 594, second column, first full paragraph). While neither Quake et al nor Urdea et al specifically teach the label amounts and the disulphide linker result in a reduction of quenching and intra-molecular thiol group formation, page 15 of the

specification states that the amount of label claimed, which is taught by Quake et al in view of Urdea et al, results in the claimed property. Therefore, the combination of the prior art has the claimed characteristic; namely, the combination reduces quenching and intra-molecular thiol group formation.

Regarding claims 20-21, the method of claim 19 is discussed above. Quake et al teach the amount of labeled derivative of the at least one nucleotide in said mixture is 19% (i.e., less than 20%; paragraph 0179), which is within the range of 5-50 mole % (i.e., claim 20) and also within the range of 10-50 mole % (i.e., claim 21).

Regarding claim 22, the method of claim 19 is discussed above. Quake et al also teach the single stranded form of said nucleic acid molecule is attached to a carrier; namely, the single stranded polynucleotide template is immobilized to the surface of a channel (paragraph 0055).

Regarding claim 23, the method of claim 22 is discussed above. Quake et al further teach the mechanism of attachment to the carrier is specific binding to biotin (paragraph 0057).

Regarding claim 24, the method of claim 23 is discussed above. Quake et al teach the carrier is a surface; namely, the surface of a channel (paragraph 0055).

Regarding claim 25, the method of claim 19 is discussed above. Quake et al also teach the label is neutralized by photobleaching (paragraph 0193).

Regarding claim 31, the method of claim 19 is discussed above. Quake et al further teach the derivative of the nucleotide is a dideoxynucleotide (paragraph 0185).

Regarding claims 33 and 38, Quake et al teach a method comprising providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186) or by photobleaching (paragraph 0193), and the removal is prior to the next extension cycle (paragraph 0216). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

While Quake et al teach the labels are fluorescent labels and that the labels are cleaved via a cleavable linker arm (paragraph 0186), Quake et al do not explicitly teach a cleavable link between the label and the nucleotide that is a disulfide (i.e., claim 33) and the linker is shorter than 8 atoms (i.e., claim 38).

However, Urdea et al teach functionally equivalent detectably labeled nucleotides (column 8, lines 20-60), wherein the detectable label is a fluorescent label (column 4,

lines 5-10) and is linked to the nucleotide with a cleavable linker in the form of a disulfide linker (i.e., claim 33; column 8, lines 20-60). The linker between the disulfide bridge and the base is less than 8 atoms; namely, Formula 13 has label R1, a disulfide for R2, x is one CH2 linker, and NH connects to the base (i.e., claim 38; column 8, lines 20-60). Urdea et al further teach that the nucleotides having the linkers and labels have the added advantage of being inexpensively synthesized in large quantity (column 2, lines 15-40). Thus, Urdea et al teach the known technique of using a disulfide as a cleavable link between a label and a nucleotide.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of labeled nucleotides attached with a cleavable linker as taught by Quake et al so that the cleavable labeled nucleotides are the functionally equivalent cleavable labeled nucleotides comprising a cleavable linker in the form of a disulfide linker (i.e., claim 33) that is less than 8 atoms (i.e., claim 38) as taught by Urdea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of having a decreased cost as a result of utilizing labels that are inexpensively synthesized in large quantity as explicitly taught by Urdea et al (column 2, lines 15-40). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et could have been applied as the labeled cleavable nucleotides in the method of Quake et al

with predictable results because the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et al predictably results in a link useful in the labeling of nucleotides.

As noted above, the prior art discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to prove that subject matter shown to be in the prior art does not posses characteristic relied on. While neither Quake et al nor Urdea et al specifically teach the label amounts and the disulphide linker result in a reduction of quenching and intra-molecular thiol group formation, page 15 of the specification states that the amount of label claimed, which is taught by Quake et al in view of Urdea et al, results in the claimed property. Therefore, the combination of the prior art has the claimed characteristic; namely, the combination reduces quenching and intra-molecular thiol group formation.

Regarding claim 34, the method of claim 33 is discussed above. Quake et al teach the label is neutralized by photobleaching (paragraph 0193).

Regarding claim 40, the method of claim 33 is discussed above. Quake et al also teach the derivative of the nucleotide is a dideoxynucleotide (paragraph 0185).

Regarding claim 42, Quake et al teach a method comprising providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled

nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed by photobleaching (paragraph 0193), and the removal is prior to the next extension cycle (paragraph 0216). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

It is noted that the claim requires either neutralizing the label or cleaving the cleavable link. Thus, the limitations regarding "the cleavage" (i.e., adding a reducing agent, exposing a thiol group, capping the thiol group) are not required when the method performs the neutralization procedure rather than the cleavage procedure.

While Quake et al teach the labels are fluorescent labels and that the labels are cleaved via a cleavable linker arm (paragraph 0186), Quake et al do not explicitly teach a cleavable link between the label and the nucleotide that is a disulfide and the linker is shorter than 8 atoms.

However, Urdea et al teach functionally equivalent detectably labeled nucleotides (column 8, lines 20-60), wherein the detectable label is a fluorescent label (column 4, lines 5-10) and is linked to the nucleotide with a cleavable linker in the form of a disulfide linker (column 8, lines 20-60). The linker between the disulfide bridge and the

base is less than 8 atoms; namely, Formula 13 has label R1, a disulfide for R2, x is one CH2 linker, and NH connects to the base (column 8, lines 20-60). Urdea et al further teach that the nucleotides having the linkers and labels have the added advantage of being inexpensively synthesized in large quantity (column 2, lines 15-40). Thus, Urdea et al teach the known technique of using a disulfide as a cleavable link between a label and a nucleotide.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of cleavable labeled nucleotides attached with a cleavable linker as taught by Quake et al so are functionally equivalent cleavable labeled nucleotides comprising the cleavable linker that is a disulfide linker that is less than 8 atoms as taught by Urdea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of having a decreased cost as a result of utilizing labels that are inexpensively synthesized in large quantity as explicitly taught by Urdea et al (column 2, lines 15-40). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et could have been applied as the labeled cleavable nucleotides in the method of Quake et al with predictable results because the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et predictably results in a link useful in the labeling of nucleotides.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not posses characteristic relied on" (205 USPQ 594, second column, first full paragraph). While neither Quake et al nor Urdea et al specifically teach the label amounts and the disulphide linker result in a reduction of quenching and intra-molecular thiol group formation, page 15 of the specification states that the amount of label claimed, which is taught by Quake et al in view of Urdea et al, results in the claimed property. Therefore, the combination of the prior art has the claimed characteristic; namely, the combination reduces quenching and intra-molecular thiol group formation.

Regarding claim 43, Quake et al teach a method consisting essentially of (i.e., comprising) providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is

extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186) or by photobleaching (paragraph 0193), and the removal is prior to the next extension cycle (paragraph 0216). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

While Quake et al teach the labels are fluorescent labels and that the labels are cleaved via a cleavable linker arm (paragraph 0186), Quake et al do not explicitly teach a cleavable link between the label and the nucleotide that is a disulfide.

However, Urdea et al teach functionally equivalent labeled cleavable nucleotides (column 8, lines 20-60), wherein the detectable label is a fluorescent label (column 4, lines 5-10) and is linked to the nucleotide with a cleavable linker in the form of a disulfide linker (column 8, lines 20-60). Urdea et al further teach that the nucleotides having the linkers and labels have the added advantage of being inexpensively synthesized in large quantity (column 2, lines 15-40). Thus, Urdea et al teach the known technique of using a disulfide as a cleavable link between a label and a nucleotide.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of cleavable labeled nucleotides attached with a cleavable linker as taught by Quake et al so that the labeled cleavable nucleotides are the functionally equivalent labeled cleavable nucleotides having a cleavable linker that is a disulfide linker as taught by

Urdea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of having a decreased cost as a result of utilizing labels that are inexpensively synthesized in large quantity as explicitly taught by Urdea et al (column 2, lines 15-40). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et al could have been applied as the labeled cleavable nucleotides in the method of Quake et al with predictable results because the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et al predictably results in a link useful in the labeling of nucleotides.

As noted above, the prior art discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to prove that subject matter shown to be in the prior art does not posses characteristic relied on. While neither Quake et al nor Urdea et al specifically teach the label amounts and the disulphide linker result in a reduction of quenching and intra-molecular thiol group formation, page 15 of the specification states that the amount of label claimed, which is taught by Quake et al in view of Urdea et al, results in the claimed property. Therefore, the combination of the prior art has the claimed characteristic; namely, the combination reduces quenching and intra-molecular thiol group formation.

Regarding claim 44, the method of claim 19 is discussed above. Quake et al teach the method is performed on beads in the form of microbeads (paragraph 0175). In addition, Quake et al teach the method is performed on beads (Example 13). Thus, modification of the method of Quake et al in view of Urdea et al results in a method performed on beads.

Regarding claim 45, the method of claim 33 is discussed above. Quake et al teach the method is performed on beads in the form of microbeads (paragraph 0175). In addition, Quake et al teach the method is performed on beads (Example 13). Thus, modification of the method of Quake et al in view of Urdea et al results in a method performed on beads.

Regarding claim 46, the method of claim 42 is discussed above. Quake et al teach the method is performed on beads in the form of microbeads (paragraph 0175). In addition, Quake et al teach the method is performed on beads (Example 13). Thus, modification of the method of Quake et al in view of Urdea et al results in a method performed on beads.

Regarding claim 47, the method of claim 43 is discussed above. Quake et al teach the method is performed on beads in the form of microbeads (paragraph 0175). In addition, Quake et al teach the method is performed on beads (Example 13). Thus, modification of the method of Quake et al in view of Urdea et al results in a method performed on beads.

16. Claims 27-28 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Urdea et al (U.S. Patent No. 4,910,300, issued 20 March 1990) as applied to claims 19 and 33 above, and further in view of Wells et al (J. Biol. Chem., vol. 261, pages 6564-6570 (1986)).

Regarding claims 27-28 and 36-37, the methods of claims 19 and 33 are discussed above in Section 15.

Neither Quake et al nor Urdea teach cleavage is performed by addition of a reducing agent to expose and provide a thiol group (i.e., claims 27 and 36) that is capped by a reagent (i.e., claims 28 and 37).

However, Wells et al teach the disulfides are cleaved with reducing agents to yield free thiol, which are capped by reaction with iodoacetamide to prevent reformation of disulfides (page 6566, column 1, last paragraph). Thus, Wells et al teach the known technique of reductively cleaving a disulfide to form a thiol group (i.e., claims 27 and 36) that is capped by a reagent (i.e., claims 28 and 37).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of disulfide linked labeled nucleotides as taught by Quake et al in view of Urdea et al so that the link is reductively cleaved to generate a thiol (i.e., claims 27 and 36) that is capped with a reagent (i.e., claims 28 and 37) as taught by Wells et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary

artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of preventing the reformation of the disulfides after cleavage as explicitly taught by Wells et al (page 6566, column 1, last paragraph). In addition, it would have been obvious to the ordinary artisan that the known technique of forming and capping an exposed thiol via reduction of a disulfide as taught by Wells et al could have been applied to the method of Quake et al in view of Urdea with predictable results because the known technique of forming and capping an exposed thiol via reduction of a disulfide as taught by Wells et al predictably results in prevention of the reformation of the disulfide link after cleavage.

17. Claims 30 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Urdea et al (U.S. Patent No. 4,910,300, issued 20 March 1990) as applied to claims 19 and 33 above, and further in view of Uemori et al (PCT International Application Publication No. WO 97/24444, published 10 July 1997), as evidenced by Atkins (Physical Chemistry. 3rd Ed., Freeman and Co., New York, 1986, page 278). Citations from Uemori et al are from the National Stage (U.S. Patent No. 6,395,526 B1, issued 28 May 2002). The National Stage is deemed an English language translation of the PCT.

Regarding claims 30 and 39, the methods of claims 19 and 33 are discussed above in Section 15.

Quake et al teach the cleavage of the linker in step c) is done with mild acid (paragraph 0186). Acidic conditions result in a pH of less than 7, as evidenced by Atkins (page 278). Thus, while Quake et al teach the cleavage portion of step c) is done at a pH below 7, Quake et al does not teach the extension with polymerase occurs at a pH below 7.

However, Uemori et al teach extension reactions of primer template/complexes using a DNA polymerase (Abstract) wherein the polymerase exhibits maximum activity at a pH of 6.5 (column 12, lines 13-16). Uemori et al also teach the DNA polymerase having the activity at pH 6.5 has the added advantage of higher primer extensibility (Abstract) with a lower error rate in DNA synthesis (column 13, lines 30-35), which improves the assay accuracy. Thus, Uemori et al teach the known technique of performing primer extension at a pH below 7.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of a DNA polymerase and cleavage of a linker at a pH below 7 as taught by Quake et al to use the DNA polymerase of Uemori et al to arrive at the instantly claimed method with a reasonable expectation of success. Use of the polymerase of Uemori et al would result in extension reactions performed at a pH 6.5. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method providing the maximum activity of the polymerase and the added advantage of higher primer extensibility with improved assay accuracy as a result of the lower error rate in DNA synthesis of the polymerase as explicitly taught by Uemori et al

(Abstract and column 13, lines 30-35). In addition, it would have been obvious to the ordinary artisan that the known technique of using the pH of Uemori et al could have been applied in step c) of the method of Quake et al in with predictable results because the known technique of using the pH of Uemori et al predictably results in a viable primer extension reaction.

18. Claims 32 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Urdea et al (U.S. Patent No. 4,910,300, issued 20 March 1990) as applied to claims 19 and 33 above, and further in view of Hyman (U.S. Patent No. 5,516,664, issued 14 May 1996).

Regarding claims 32 and 41, the methods of claims 19 and 33 are discussed above in Section 15.

While Quake et al teach a label that is cleaved (paragraph 0186), Quake et al do not teach a functionally equivalent label is cleaved using an agent in the form of alkaline phosphatase.

However, Hyman teaches the extension of a primer using a functionally equivalent blocked nucleotide, wherein the blocking group is removed with an agent in the form of a phosphatase (Abstract); namely, alkaline phosphatase (Example 5). Thus, Hyman teaches the known technique of extending a nucleic acid with a label that is removed using an agent in the form of alkaline phosphatase.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method of Quake et al so that the blocking label is the functionally equivalent label that is cleaved using an agent in the form of alkaline phosphatase as taught by Hyman to arrive a the instantly claimed method with a reasonable expectation of success. It would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent label that is cleaved using an agent in the form of alkaline phosphatase as taught by Hyman could have been applied as the label in the method of Quake et al in with predictable results because the known technique of using the functionally equivalent label that is cleaved using an agent in the form of alkaline phosphatase as taught by Hyman predictably results in a functionally equivalent label for blocking a primer extension reaction.

19. Claims 42 and 46 rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Urdea et al (U.S. Patent No. 4,910,300, issued 20 March 1990) in view of Wells et al (J. Biol. Chem., vol. 261, pages 6564-6570 (1986)).

It is noted that while claims 42 and 46 have been rejected under 35 U.S.C 103(a) as described above in Section 15, the claims are also obvious using the interpretation outlined below.

Regarding claim 42, Quake et al teach a method comprising providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is

hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186). The removal is prior to the next extension cycle (paragraph 0216). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

While Quake et al teach the labels are fluorescent labels and that the labels are cleaved via a cleavable linker arm (paragraph 0186), Quake et al do not explicitly teach a cleavable link between the label and the nucleotide that is a disulfide and the linker is shorter than 8 atoms.

However, Urdea et al teach detectably labeled nucleotides (column 8, lines 20-60), wherein the detectable label is a fluorescent label (column 4, lines 5-10) and is linked to the nucleotide with a cleavable linker in the form of a disulfide linker (column 8, lines 20-60). The linker between the disulfide bridge and the base is less than 8 atoms; namely, Formula 13 has label R1, a disulfide for R2, x is one CH2 linker, and NH

connects to the base (column 8, lines 20-60). Urdea et al further teach that the nucleotides having the linkers and labels have the added advantage of being inexpensively synthesized in large quantity (column 2, lines 15-40). Thus, Urdea et al teach the known technique of using a disulfide as a cleavable link between a label and a nucleotide.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of labeled cleavable nucleotides attached with a cleavable linker as taught by Quake et al so that the labeled cleavable nucleotides are the functionally equivalent labeled cleavable nucleotides comprising a cleavable linker that is a disulfide linker that is less than 8 atoms as taught by Urdea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of having a decreased cost as a result of utilizing labels that are inexpensively synthesized in large quantity as explicitly taught by Urdea et al (column 2, lines 15-40). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent labeled cleavable nucleotides of Urdea et al could have been applied as the labeled cleavable nucleotides in the method of Quake et al with predictable results because the known technique of using the functionally equivalent labeled cleavable nucleotides of Urdea et al predictably results in a link useful in the labeling of nucleotides.

While Quake et al teach the label is then removed by cleaving the cleavable link (paragraph 0186), neither Quake et al nor Urdea teach cleavage is performed by addition of a reducing agent to expose and provide a thiol group that is capped by a reagent.

However, Wells et al teach the disulfides are cleaved with reducing agents to yield free thiol, which are capped by reaction with iodoacetamide to prevent reformation of disulfides (page 6566, column 1, last paragraph). Thus, Wells et al teach the known technique of reductively cleaving a disulfide to form a thiol group that is capped by a reagent.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of disulfide linked labeled nucleotides as taught by Quake et al in view of Urdea et al so that the link is reductively cleaved to generate a thiol that is capped with a reagent as taught by Wells et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of preventing the reformation of the disulfides after cleavage as explicitly taught by Wells et al (page 6566, column 1, last paragraph). In addition, it would have been obvious to the ordinary artisan that the known technique of forming and capping an exposed thiol via reduction of a disulfide as taught by Wells et al could have been applied to the method of Quake et al in view of Urdea with predictable results because the known technique of forming and capping an exposed thiol via reduction of

a disulfide as taught by Wells et al predictably results in prevention of the reformation of the disulfide link after cleavage.

Regarding claim 46, the method of claim 42 is discussed above. Quake et al teach the method is performed on beads in the form of microbeads (paragraph 0175). In addition, Quake et al teach the method is performed on beads (Example 13). Thus, modification of the method of Quake et al in view of Urdea et al and Wells et al results in a method performed on beads.

Response to Arguments

20. Applicant's arguments filed 9 November 2009 (hereafter the "Remarks") have been fully considered but they are not persuasive for the reasons discussed below.

A. Applicant argues on page 15 of the Remarks that the trade names are permissible.

However, it is noted that MPEP 608.01(v) (cited by Applicant on page 15 of the Remarks) also states that the conditions regarding trade names must be met at the time of filing of the complete application. Applicant did not meet this condition at the time of filing the complete application.

In addition, as noted above, it is reiterated that pages 258 and 262 of the Sigma "Products for Life Science Research" Catalog (2000-2001; provided with this Office Action by the examiner) properly establish the chemical structures of Tween 20 and Triton X-100 at the time of filing. Applicant is encouraged to use the evidence

presented in the 2000-2001 Sigma "Products for Life Science Research" Catalog for future amendments regarding Tween 20 and Triton X-100.

It is also reiterated that given the ambiguity regarding the chemical structure of NP 40 at the time of filing of the instant Application (as evidenced by page 348 of the 1998 Calbiochem general catalog and the Material Safety Data Sheet (MSDS) provided online by aktasdis.com), it is suggested that Applicant provide evidence of the source(s) of NP 40 used in the practice of the claimed invention so as to clearly establish the chemical structure of the compound(s) used in practicing the instantly claimed method.

B. Applicant argues on pages 16-18 of the Remarks that there is no teaching in Quake et al of a percentage range of labeled nucleotide to address the problems of quenching and intra-molecular disulfide bond formation characteristic of a fluorophore nucleotide with a disulphide linker.

However, as noted above, and in the previous Advisory Action, the prior art discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to prove that subject matter shown to be in the prior art does not posses characteristic relied on. While neither Quake et al nor Urdea et al specifically teach the label amounts and the disulphide linker result in a reduction of quenching and intra-molecular thiol group formation, page 15 of the specification states that the amount of label claimed, which is taught by Quake et al in view of Urdea et al, results in the claimed property. Therefore, the combination of the prior art has the

claimed characteristic; namely, the combination reduces quenching and intra-molecular thiol group formation.

In response to applicant's argument that the claimed combination reduces quenching and intra-molecular thiol group formation, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

C. Applicant argues on pages 17-18 of the Remarks that the molecules of Quake et al do not possess the steric freedom to perform this chemistry. Thus, Applicant argues the prior art of Quake et al individually.

However, Applicant provides no evidence of a lack of steric freedom. MPEP 716.01(c) makes clear that "[t]he arguments of counsel cannot take the place of evidence in the record" (*In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965)). Thus, Applicant's mere arguments that that the molecules of Quake et al do not possess the steric freedom to perform this chemistry cannot take the place of evidence in the record.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further, it is noted that the linkers of Urdea et al meet the limitations of the claims as described above in the rejections; thus, the modification of the method of Quake et al with the teachings of Urdea et al would result in molecules that do possess the steric freedom to perform the argued chemistry.

D. Applicant argues on page 18 of the Remarks that Urdea et al do not address the problems of quenching and intra-molecular disulfide bond formation characteristic of a fluorophore nucleotide with a disulphide linker

However, as noted above, while neither Quake et al nor Urdea et al specifically teach the label amounts and the disulphide linker result in a reduction of quenching and intra-molecular thiol group formation, page 15 of the specification states that the amount of label claimed, which is taught by Quake et al in view of Urdea et al, results in the claimed property. Therefore, the combination of the prior art has the claimed characteristic; namely, the combination reduces quenching and intra-molecular thiol group formation.

Further, it is reiterated that in response to applicant's argument that the claimed combination reduces quenching and intra-molecular thiol group formation, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious.

E. Applicant agues on page 18 of the Remarks that claims 22-24 and new claims 44-47 are directed to a carrier that can be a gel, a bead, a surface or a fiber, rather that a synthesis channel as taught by Quake et al.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a gel, a bead, or the surface of a fiber) are not recited in rejected claims 22-23. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

With respect to claim 24, the claim encompasses a method wherein the carrier is "a surface," which encompasses a surface within a synthesis channel. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding "a surface" (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]).

In addition, with respect to claims 44-47, it is reiterated that Quake et al teach the method is performed on beads in the form of microbeads (paragraph 0175). Further, Quake et al teach the method is performed on beads (Example 13). Thus, modification of the method of Quake et al in view of Urdea et al results in a method performed on beads.

F. Applicant argues on page 18 of the Remarks that independent claim 43 utilizes the more restrictive claim language "consisting essentially of."

However, a review of the specification yields no limiting definition of "consisting essentially of." Thus, as noted above, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See MPEP 2163.

G. Applicant argues on page 19 of the Remarks that the alleged advantage regarding quenching and intramolecular thiol formation is unrecognized in the art.

However, MPEP 2145 II clearly states that "[m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention" (*In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA1979)). Further, MPEP 2145 II also states that with respect to *Ex parte Obiaya* (227 USPQ 58, 60 (Bd.Pat. App. & Inter. 1985) (The prior art taught combustion fluid analyzers which used labyrinth heaters to maintain the samples at a uniform temperature. Although appellant showed an unexpectedly shorter response time was obtained when a labyrinth heater was employed, the Board held this advantage would flow naturally from following the suggestion of the prior art.). Thus, following the teaching of the prior art of Quake et al regarding the amount of label used, and following the suggestion of the prior art of Urdea et al to use the thiol linkers, the alleged advantage regarding quenching and intramolecular thiol formation would flow naturally from the teachings of the prior art.

H. Applicant also argues on pages 19-20 of the Remarks that accidental results do not constitute anticipation.

However, the claims are rejected as obvious, not as anticipated. Thus, Applicant's arguments regarding anticipation are moot in view of the rejections of the claims as obvious.

I. Applicant argues on pages 19-20 of the Remarks that the claimed invention produces unexpected results, that the mere fact that a certain thing may result

from a set of circumstances in not sufficient to prove inherency and that occasional results are not inherent.

However, Applicant's arguments rely upon the data presented in Figures 5-8 (based on the experimental procedure detailed in Example 4 of the instant specification). As noted in the previous Advisory Action, the data used to illustrate the alleged "occasional results" arises "from a set of circumstances" that is not commensurate in scope with the instant claims for the following reasons:

i. The data is limited to specific biotinlyated, fluorescein labeled oligonucleotides immobilized on streptavidinated beads; neither the specific oligonucleotides, biotin, fluorescein, nor streptavidinated beads are required by the instant claims.

ii. The data is limited to specific buffers, temperatures, volumes and concentrations of reagents, as well as specific reaction steps (e.g., washing with TENT buffer); none of these limitations are required by the instant claims.

iii. The data is limited to Cy5-SS-dNTPs, whereas the claim encompasses any labeled nucleotide having a fluorophore and a disulfide bond.

iv. The data is limited to Klenow exo- polymerase, whereas the claim encompasses the use of any polymerase.

v. The data is based on a pyrosequencing step not required by the instant claims.

Therefore, the method having the alleged unexpected results is not commensurate in scope with the instant claims, nor has Applicant demonstrated that the alleged unexpected results are a direct result of the invention as claimed. Therefore,

the claims remain rejected as obvious over the prior art for the reasons cited above. See MPEP 716.02(d)[R-2].

J. Applicant argues on pages 20-21 of the Remarks that the alleged unexpected results have probative weight.

However, the examiner has carefully considered the weight of Applicant's arguments. As noted above, Applicant has not demonstrated that the alleged unexpected results are a direct result of the invention as claimed. Applicant's allegations of unexpected results appear to be obtained solely from the method as practiced by Example 4. Applicant has not demonstrated that the alleged unexpected results would be obtained using other labels, other disulfide linkers, non-biotinlyated oligonucleotides, other buffer conditions, etc., as woould be encompassed by the invention as claimed. Therefore the claims remain rejected for the reasons discussed above.

Conclusion

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571)272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert T. Crow
Examiner
Art Unit 1634

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Examiner, Art Unit 1634